REMARKS

1. Interview Conducted February 19, 2008.

Applicant thanks the Examiner and her supervisor for their time on August 26, 2008. Applicant appreciates being allowed to explain the distinctions between drug-induced nephrotoxicity and other types of nephropathies. Applicant herein provides further support for the distinctions previously made.

2. Request for Continued Examination.

Applicant appreciates the Examiner's acknowledgement of Applicant's Request for Continued Examination ("RCE") under 37 CFR 1.114, including the fee as set forth in 37 CFR 1.17(e). Applicant also appreciates the Examiner's withdrawal of the finality of the previous Office Action in light of the timely complete filing of the RCE.

3. Claim Amendments

Claims 1, 5, 9, 13 and 21 are herein amended without prejudice or disclaimer of the subject matter therein. No new matter has been added by such amendments. Applicant made all amendments to clarify that the therapeutic methods of claims 1, 5, 9, 13 and 21 were directed to drug-induced nephrotoxicity in general. This is the state of the claim as originally-filed.

4. Withdrawal of Rejection of Claims 1-21 under 35 U.S.C. 112, first paragraph.

In order to expedite allowance of claims, and without prejudice or disclaimer of the subject matter thereof, Applicant previously amended Claims 1, 5, 9, 13, and 21 to exclude the term, "preventing". Applicant acknowledges the Examiner's withdrawal of the rejection of claims 1-21 under 35 U.S.C. 112, first paragraph.

5. Rejection of Claims under 35 U.S.C. 103(a)

The Examiner rejected claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a) for the reasons of record.

Specifically, the Examiner cites Tofovic et al. to argue that it shows that chronic treatment with 2-hydroxyestradiol (2-OHE) significantly reduces symptoms of nephropathy, such as proteinuria, glomerulosclerosis and interstitial inflammation in male obese rats..."

Applicant respectfully traverses this rejection. Applicant submits that the Examiner has not established a prima facie case of obviousness with regards to the teachings of Tofovic et al. The Examiner acknowledges that, "Tofovic et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17 and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of [whether] it is a drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results." The Examiner then erroneously concludes that, "[r]egardless of how the kidney disease originated, it is obvious that the treatment would effectively treat a kidney disease regardless of [whether] it is drug-induced or naturally occurring." However, the Examiner also states, "[u]nless Applicants can show data that contradicts this, it remains obvious to a person of ordinary skill in the art that treatment of a kidney disease would be the same regardless of its etiology."

Applicant herein will explain how drug-induced nephrotoxicity is distinct from other nephropathies. As an initial matter, the most definitive text on nephrology is the two-volume set entitled, "Seldin and Giebisch's, The Kidney Physiology and Pathophysiology." The fourth edition was recently published this year and is 2800 pages long. Applicant would like to point out that Section IV of this text (pages 2113-2613) entitled, "Pathophysiology of Renal Disease" includes a subsection entitled, "Mechanisms of Renal Injury (Pages 2143-2535). In this section, there are more than 500 pages describing the different mechanisms of renal injury and another 392 pages referencing thousands of articles that describe the same. Chapter 87 entitled, "Cellular Mechanisms of Drug Nephrotoxicity" is entirely devoted to the causes of nephrotoxicity and is 28 pages long and includes 479 references on the subject. Applicant references this two-volume set in order to point out that the mechanisms associated with various kidney diseases, including

nephrotoxicity, are complex. There would be no need for this magnus opus if the mechanism for all kidney diseases were the same.

Applicant also respectfully asserts the mechanisms associated with causing drug-induced nephrotoxicity are cell necrosis and apoptosis. (See p. 2511-2518). This is in contrast with other kidney diseases that are caused by different mechanisms. For instance, renal vasculitis, glomerular diseases and renal interstitial diseases are all caused by immunological and inflammatory injury. Diabetes-induced renal injury is caused by excessive cell growth with cell hypertrophy, cell proliferation and extracellular matrix production. In turn, ischemic renal disease, renal failure in cirrhosis and renal disease associated with pregnancy are all caused by a reduction in the blood flow to the kidney. These are but a few examples of the distinct causes of a variety of kidney diseases in order to show that it simply is not true that "pathologies of the kidney would display the same symptoms regardless of [whether] it is a drug-induced or natural occurrence." Additionally, as the cause is distinct for each of the exemplified kidney diseases, so is the treatment. As such, it is also not true that "treatment of a kidney disease would be the same regardless of its etiology."

Applicant acknowledges the article cited by the Examiner, "Assessment of Nephrotoxicity" by L.F. Prescott ("Prescott"). This summary article describes the various clinical indicators associated with nephrotoxicity. Prescott acknowledges that, "[r]enal histology probably provides the best index of nephrotoxicity..." and that supports the premise that all kidney diseases are not the same as histological results of renal biopsies are crucial in diagnosing a particular kidney disease. If all kidney diseases were the same, the histological results of renal biopsies would not be critical when diagnosing a kidney disease. The Examiner further states that, "[t]he main difference between nephropathies and nephrotoxicity is that conventional clinical investigation of renal function is of limited value in nephrotoxicity." This is erroneous as kidney diseases are extremely complex and caused by a wide-variety of mechanisms and, in light of that fact, conventional clinical parameters are not useful in diagnosing the majority of kidney diseases.

The Examiner further states, "[h]owever, there is no apparent difference between the actual condition, i.e. proteinuria, regardless of its etiology." Although Applicant agrees that

proteinuria may be caused by a nephrotoxic agent, Applicant does not agree that its treatment is the same, regardless of the particular kidney disease at issue. For example, it is well known that ciclosporin A (CsA) causes nephrotoxicity. Once a patient displays symptoms of nephrotoxicity, the estradiol metabolites of the present invention may be administered to treat proteinuria in such a patient. In contrast, a patient with idiopathic membranous nephropathy that typically presents with proteinuria may be treated with CsA (see enclosed Goumenos reference). If a patient with nephrotoxicity were to be given this same agent, it would not treat the proteinuria and would actually work to increase it. As such, it is simply not true that there is "no apparent difference between the actual condition (herein proteinuria) regardless of its etiology" as the cause of the condition is key to determining the appropriate treatment.

Applicant respectfully points out that in order to establish a prima facie case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When an independent claim is deemed nonobvious under 35 U.S.C. 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant respectfully submits that the Examiner has not overcome this burden. Specifically, Tofovic et al. does not teach that the conditions being treated are drug-induced and, accordingly, the Examiner has not overcome the aforementioned burden since each and every one of the claim limitations of the instant invention were not taught or suggested by Tofovic et al.

Furthermore, the Examiner has the burden to prove that the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. All of the claims rejected by the Examiner in this office action contemplate treating various drug-induced conditions and in no way are associated with, "the development of renal disease in genetic nephropathy associated

with obesity and the metabolic syndrome." The mechanisms (or etiologies) associated with genetic nephropathy when compared to nephrotoxicity are very different. As Applicant stated above, the mechanisms associated with causing drug-induced nephrotoxicity are cell necrosis and apoptosis, which are not the causes of genetic nephropathy. In no way does Tofovic et al. suggest modifying its teachings in order to treat the conditions mentioned nor does Tofovic et al. suggest that its teachings would also be effective in treating drug-induced conditions. Therefore, Applicant respectfully submits that the Examiner has failed to show that Tofovic et al. contains some suggestion or incentive to modify its teachings in order to treat the drug-induced conditions of the instant application.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden. Therefore, Applicant fails to see how a person of ordinary skill in the art would have a reasonable expectation of success in modifying Tofovic et al. to treat the drug-induced conditions of the instant application.

The Examiner has also cited Xiao et al. to argue it shows that the growth of glomerular mesangial cells is associated with the pathogenesis of renal disease. The Examiner acknowledges that Xiao et al. does not teach the conditions listed in claims 1, 2, 9, 13, 17 and 21 are drug-induced but concludes "the pathologies of the kidney would display the same symptoms regardless of [whether] it is drug-induced or a natural occurrence so the treatment with the estradiol metabolites would have the same results."

Applicant respectfully traverses this rejection. Applicant submits that that the pathologies of the kidney are **not** the same across a wide-variety of kidney diseases, including nephrotoxicity. (emphasis added) As discussed above, the kidney is a complex organ with a multitude of mechanisms associated with various diseases. Treatment of the various disease-associated conditions, such as proteinuria, is also very different depending on the disease associated with it. If all renal diseases and treatment of all such diseases were alike, there would be no need for the two-volume set entitled, "The Kidney," no need for renal biopsies and no need

for nephrologists to tailor treatments according to the histological results of those biopsies. Applicant respectfully gave a specific example above relating to CsA.

The Examiner has also cited Tofovic et al. and Xiao et al. in view of Allison et al. to argue that although Tofovic et al. and Xiao et al. do not teach a controlled release formulation, Allison teaches a device that is capable of sustained release of the active ingredient. Accordingly, the Examiner argues, it would have been obvious to combine the teachings of Tofovic et al. and Xiao et al. with Allison.

The Examiner submitted that Tofovic et al. and Xiao do not teach a controlled release formulation but as Applicant has pointed out above, there are many other things that those references do not teach. Illustratively, Tofovic et al. does not teach treating the drug-induced conditions of the instant application. Further, Xiao actually teaches away from the instant invention because it teaches that 2-hydroxyestradiol does not induce NO synthesis thus it would not protect against the progression of renal disease. Additionally, it is false to assume that because "these pathologies of the kidney would display the same symptoms regardless of [whether] it is drug-induced or a natural occurrence" that "treatment with estradiol metabolites would have the same results." Since Xiao teaches away from the instant invention, it cannot properly be used in a 35 U.S.C. 103(a) rejection. Therefore, there is no motivation to combine these references with Allison because both Xiao and Tofovic are incorrectly cited as proper 35 U.S.C. 103(a) prior art.

As previously stated in this Response, the Examiner has the burden to show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Even after combining Tofovic et al. and Xiao et al. with Allison, the Examiner has not satisfied the aforementioned burden since none of the references suggest or teach preventing the conditions of the instant invention nor do they teach or suggest treating or preventing the drug-induced conditions of the instant invention.

As such, Applicant believes all of the Rejections under 35 U.S.C. 103(a) are improper and respectfully request that at this point they be removed and the claims be allowed. Applicant's arguments above are responsive to prior arguments made by the Examiner and are

sufficient to explain to the Examiner why the cited references are insufficient to make the invention obvious.

6. Concluding Remarks

In view of the foregoing, Applicant respectfully submits that all rejections under 35 U.S.C. 103(a) have been overcome. Accordingly, Applicant believes that Claims 1-24 are now in a condition for allowance. In the event the Examiner has any questions regarding the Applicant's position, a telephone call to the undersigned representative is requested.

Respectfully Submitted,

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Date

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